American Journal of Biomedical Science & Research

www.biomedgrid.com

ISSN: 2642-1747

Mini Review

Central Nervous System Disease Treatment Development Using Human Fetal-derived Neural Stem Cells/ Neural Progenitor Cells

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To Cite This Article: *Yu Mi Park. Central Nervous System Disease Treatment Development Using Human Fetal-derived Neural Stem Cells/ Neural Progenitor Cells. Am J Biomed Sci & Res. 2022 - 16(5). AJBSR.MS.ID.002266.* DOI: 10.34297/AJBSR.2022.16.002266

Received: June 24, 2022; **Published:** July 04, 2022

Keywords: Human fetal tissue research, Neural Stem Cell, Neural Progenitor Cells, Central Nervous System, Spinal Cord Injury, Alzheimer's Disease, Parkinson's Disease

Introduction

Neural Stem Cells (NSCs) and Neural Progenitor Cells (NPCs) isolated from human fetuses are an attractive source for cell therapy for almost all Central Nervous System (CNS) diseases without the need for special treatments [1-3]. Human NSCs/NPCs are widely distributed in the fetal forebrain, Sub-Granular Zone (SGZ), Subventricular Zone (SVZ), and the dentate gyrus of the hippocampus in the adult brain [4,5]. NSCs/NPCs self-renew by proliferating in an undifferentiated state and can differentiate into neurons, oligodendrocytes, and astrocytes [6]. Damaged cells do not regenerate in mammals with CNS diseases, including humans. Transplanted NSCs/NPCs proliferate and continue to differentiate into neuronal and glial cells.

The resulting neuro-regeneration may serve as a curative treatment for CNS diseases. Research, development, and human clinical trials require homologous NSCs/NPCs and other sources of NSCs/NPCs. NSCs/NPCs are the best raw materials for cell therapy for treating CNS diseases, including Alzheimer's Disease (AD), Parkinson's Disease (PD), Spinal Cord Injury (SCI), Amyotrophic Lateral Sclerosis (ALS), and stroke. Most studies on CNS diseases use NSCs/NPCs isolated from the brain or spinal cord of embryonic mice [7,8]. However, clinical trials require human allogenic NSCs/NPCs. Human-derived NSCs/NPCs can be obtained in various ways [3,9-14].

There are three main types of Pluripotent Stem Cells (PSCs). Embryonic Stem Cells (ESCs) isolated from blastocysts are relatively easy to establish. ESCs are highly effective and can differentiate into all cell types. Therefore, there are no restrictions on diseases that can be treated using ESCs. Also, they have high market scalability. However, ethical concerns are associated with the use of embryonic tissues [10,11]. Reprogramming somatic cells into pluripotent ESCs by somatic cell nuclear transfer allows for mass production of cells with no immune rejection. However, ethical problems remain: the process uses eggs and there is still the possibility of cancer.

The second type of PSCs is induced PSCs (iPSCs). These can be obtained through reverse differentiation using well-established methods. Therapeutic efficacy is pronounced as there are no restrictions on diseases that can be treated. Market scalability is the highest of all PSCs and there are no ethical or immune

rejection problems. However, there is a possibility of cancer, and the stability of the introduced foreign genes is continuously being investigated [12,13]. Mesenchymal Stem Cells (MSCs) are the third PSC type. They were first identified in the bone marrow [15] and subsequently in other locations, including umbilical cord tissue [16,17], umbilical cord blood [18], adipose tissue [19,20], skin [21], the dental pulp [22], and pancreas [23]. Adult MSCs can be both allogeneic and autologous. Both can be separated directly from the adult tissues and are relatively easy to obtain. Many methods have already been developed for MSCs, which permit easy acquisition, reduce ethical concerns, and the likelihood of immune rejection.

However, mass production is difficult, and if autologous MSCs are not used, immune rejection may occur. Treatment efficiency is low for autologous and allogeneic MSCs, and diseases amenable to treatment can be limited. Market expansion for autologous MSCs is the lowest of all PSCs because of the one-to-one approach but is relatively high for allogeneic MSCs because the cells can be used in many immune-compatible patients [15,21,24]. Neurogenesis is limited in healthy adult mammals [9,25,26]. In contrast, brain tissue derived NSCs/NPCs, a representative adult mammalian tissue isolated from the adult brain, can continue to proliferate in vitro. During nerve transplantation, cells become integrated into cell survival, migration, and the host CNS. No tumors have yet been reported [27]. NSCs/NPCs implanted into the brain of an animal model with degenerative neurological disease differentiate into appropriate neurons in response to a microenvironmental or a disease-specific signal, regenerating damaged neurons [28-30]. Transplanted NSCs/NPCs specifically move to nerve damage sites and migrate extensively across the entire neural axis, providing cells, neurotrophic factors, neurotransmitters, axons, extracellular substrates, and cell-adhesive molecules to induce neurogenesis and angiogenesis [31].

Fetal-derived NSCs/NPCs were obtained from medically (and legally) aborted fetuses. While the origin of the cells can be ethically contentious, the cells displayed the best growth and differentiation rates among all NSCs/NPCs. The donation of aborted fetuses was restricted. Furthermore, since it is difficult even for experts with professional anatomical knowledge to separate the brain and spinal cord according to fetal development, the availability and use of fetal-derived NSCs/NPCs can be globally restricted [1,32-34]. In addition, cell viability and composition vary from donor to donor, and the likelihood of immunological rejection or contamination can increase with the heterogeneity of donor cells [1].

Clinical trials for various CNS diseases, including SCI, PD, AD, MS, ALS, and stroke, have used primary fetal brain and spinal cord tissue derived NSCs/NPCs. These trials demonstrate that therapy with NSCs may be suitable for neurodegenerative diseases [35,36]. The status of clinical trials on targeted NSC/NPC therapy for intractable CNS diseases is available at the National Library of Medicine (ClinicalTrials.gov). A total of 37 clinical trials based on human fetal-derived NSCs/NPCs are currently in progress. In one trial, 23 patients were administered fetal-derived NSCs/NPCs (23%) and 10 patients received gene therapy using fetal-derived NSCs/NPCs (27%). Two clinical trials used ESC-NSCs (5%), one used porcine PSC-NSCs (2%), and one used iPSC-NSCs (2%). NSCs/NPCs derived from human fetuses have often been used as treatments. Clinical trials involving NSCs/NPCs most often target SCI, whereas glioma is the most common target for clinical trials involving NSC/NPC-based gene therapy [3]. As expected, the most common CNS disease targets are SCI, stroke, PD, and ALS [3,35].

In addition to the aforementioned fetal-derived NSCs/NPCs, clinical trials for CNS are underway with various other types of stem cells. However, these treatments are not yet commercially available. As human fetal NSCs/NPCs are superior to other raw materials, research following the establishment of a separation culture technique is important. Many studies are required before the clinical application of human NSCs/NPCs could be realized. During the development of the neurological system, a method to develop neurological stem cells is used to identify the differentiation, neurogenic, and regenerative mechanisms of NSCs/NPCs. Studies are needed to evaluate the appropriateness and economics of stem cell therapy, develop functional transplants according to the pathophysiology of each refractory neurological disease, identify the effects of cell transplantation in disease models, clarify long-term side effects, and identify protective agents. Strategic developmental research aimed at applying treatments together is necessary [33,37].

The research will need to encompass all the processes such as chemistry, manufacturing, and control (CMC), the clinical application of NSCs/NPCs, and the non-clinical tests (such as potency tests, distribution tests, toxicity tests, and oncogenicity tests). Effective cell lines have been established at a laboratory level. To utilize these cell lines as stem cell treatments, data on the safety of these treatments must be secured and approved by regulatory agencies such as the Food and Drug Administration [3,38]. At the laboratory level, studies have been performed using various animal models or cells to confirm the therapeutic efficacy of cultured cells. These studies have revealed the treatment mechanisms. The findings are published in peer-reviewed literature. However, evaluating efficacy from the perspective of commercialization is the starting point of cell therapy development. The development of treatments for nerve tissue regeneration should continue, given that damaged nerve tissues cannot be regenerated. It is not guaranteed that CNS cell therapies based on NSCs/NPCs, currently under development, will ultimately prove to be safe treatments with significant benefits for patients.

For the clinical application of cell therapies for CNS disorders, the availability of continuous and standardized clinical-grade stem cells following current good manufacturing practice guidelines that can combine the plasticity of human fetal-derived NSCs/NPCs with extensive proliferative capabilities and functional stability will be crucial [1].

References

1. Ferrari D, Gelati M, Profico DC, Vescovi AL (2018) Human fetal neural stem cells for neurodegenerative disease treatment. Results Probl Cell Differ 66: 307-329.
2. Grochowski C, Radzikowska E, Maciejewski R (2018) Neural stem cell therapy-Brief review. Clin Neurol Neurosurg 173: 8-14.
3. Fernandez-Muñoz B, Garcia-Delgado AB, Arribas-Arribas B, Sanchez-Pernaute R (2021) Human neural stem cells for cell-based medicinal products. Cells 10(9): 2377.
4. Yamaguchi M, Seki T, Imayoshi I, Tamamaki N, Hayashi Y, et al. (2016) Neural stem cells and neuro/gliogenesis in the central nervous system: Understanding the structural and functional plasticity of the developing, mature, and diseased brain. J Physiol Sci 66(3): 197-206.
5. Obernier K, Alvarez Buylla A (2019) Neural stem cells: Origin, heterogeneity, and regulation in the adult mammalian brain. Development 146(4): dev156059.
6. De Filippis L, Binda E (2012) Concise review: Self-renewal in the central nervous system: Neural stem cells from embryo to adult. Stem Cells Transl Med 1: 298-308.
7. Homayouni MF, Sadeghi Zadeh M, Alizadeh SB, Dehghani VR, Narimani S, et al. (2018) Isolation and culture of embryonic mouse neural stem cells. J Vis Exp 141: e58874.
8. Ou Y, Che M, Peng J, Zhou M, Wu G, et al. (2022) An efficient method for the isolation and cultivation of hypothalamic neural stem/progenitor cells from mouse embryos. Front Neuroanat 16: 711138.
9. Boese AC, Le QE, Pham D, Hamblin MH, Lee JP, et al. (2018) Neural stem cell therapy for subacute and chronic ischemic stroke. Stem Cell Res Ther 9(1): 154.
10. Yoon SH, Bae MR, La H, Song H, Hong K, et al. (2021) Efficient generation of neural stem cells from embryonic stem cells using a three-dimensional differentiation system. Int J Mol Sci 22(15): 8322.
11. Zarei-Kheirabadi M, Sadrosadat H, Mohammadshirazi A, Jaberi R, Sorouri F, et al. (2020) Human embryonic stem cell-derived neural stem cells encapsulated in hyaluronic acid promotes regeneration in a contusion spinal cord injured rat. Int J Biol Macromol 148: 1118-1129.
12. Blelloch R, Wang Z, Meissner A, Pollard S, Smith A, et al. (2006) Reprogramming efficiency following somatic cell nuclear transfer is influenced by the differentiation and methylation state of the donor nucleus. Stem Cells 24(9): 2007-2013.
13. Gage FH, Temple S (2013) Neural stem cells: Generating and regenerating the brain. Neuron 80(3): 588-601.
14. Nam H, Lee KH, Nam DH, Joo KM (2015) Adult human neural stem cell therapeutics: Current developmental status and prospect. World J Stem Cells 7(1): 126-136.
15. Friedenstein AJ, Piatetzky-Shapiro II, Petrakova KV (1966) Osteogenesis in transplants of bone marrow cells. J Embryol Exp Morphol 16(3): 381-390.
16. Mcelreavey KD, Irvine AI, Ennis KT, Mc Lean WH (1991) Isolation, culture and characterisation of fibroblast-like cells derived from the Wharton's jelly portion of human umbilical cord. Biochem Soc Trans 19(1): 29S.
17. Park YM, Lee M, Jeon S, Hrůzová D (2021) In vitro effects of conditioned medium from bioreactor cultured human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) on skin-derived cell lines. Regen Ther 18: 281-291.
18. Park SI, Lim JY, Jeong CH, Kim SM, Jun JA, et al. (2012) Human umbilical cord blood-derived mesenchymal stem cell therapy promotes functional recovery of contused rat spinal cord through enhancement of endogenous cell proliferation and oligogenesis. J Biomed Biotechnol 2012: 362473.
19. Qin Y, Zhou C, Wang N, Yang H, Gao WQ (2015) Conversion of adipose tissue-derived mesenchymal stem cells to neural stem cell-like cells by a single transcription factor, Sox2. Cell Reprogram 17(3): 221-226.
20. Hernández R, Jiménez LC, Perales AJ, Perazzoli G, Melguizo C, et al. (2020) Differentiation of human mesenchymal stem cells towards neuronal lineage: Clinical trials in nervous system disorders. Biomol Ther (Seoul) 28(1): 34-44.
21. Urrutia DN, Caviedes P, Mardones R, Minguell JJ, Vega-Letter AM, et al. (2019) Comparative study of the neural differentiation capacity of mesenchymal stromal cells from different tissue sources: An approach for their use in neural regeneration therapies. PLOS ONE 14: e0213032.
22. Arimura Y, Shindo Y, Yamanaka R, Mochizuki M, Hotta K, et al. (2021) Peripheral-neuron-like properties of differentiated human dental pulp stem cells (hDPSCs). PLOS ONE 16(5): e0251356.
23. Seeberger KL, Eshpeter A, Korbutt GS (2011) Isolation and culture of human multipotent stromal cells from the pancreas. Methods Mol Biol 698: 123-140.
24. Chen S, Zhang W, Wang JM, Duan HT, Kong JH, et al. (2016) Differentiation of isolated human umbilical cord mesenchymal stem cells into neural stem cells. Int J Ophthalmol 9(1): 41-47.
25. Elder GA, De Gasperi R, Gama Sosa MAG (2006) Research update: Neurogenesis in adult brain and neuropsychiatric disorders. Mt Sinai J Med 73(7): 931-940.
26. Liu YP, Lang BT, Baskaya MK, Dempsey RJ, Vemuganti R, et al. (2009) The potential of neural stem cells to repair stroke-induced brain damage. Acta Neuropathol 117(5): 469-480.
27. Okano H, Sawamoto K (2008) Neural stem cells: Involvement in adult neurogenesis and CNS repair. Philos Trans R Soc Lond B Biol Sci 363(1500): 2111-2122.
28. Suzuki H, Imajo Y, Funaba M, Nishida N, Sakamoto T, et al. (2021) Current concepts of neural stem/progenitor cell therapy for chronic spinal cord injury. Front Cell Neurosci 15: 794692.
29. Baker EW, Kinder HA, West FD (2019) Neural stem cell therapy for stroke: A multimechanistic approach to restoring neurological function. Brain Behav 9(3): e01214.
30. Rahman MM, Islam MR, Islam MT, Harun Or Rashid M, Islam M, et al. (2022) Stem cell transplantation therapy and neurological disorders: Current status and future perspectives. Biology 11(1): 147.
31. Kaminska A, Radoszkiewicz K, Rybkowska P, Wedzinska A, Sarnowska A (2022) Interaction of neural stem cells (NSCs) and mesenchymal stem cells (MSCs) as a promising approach in brain study and nerve regeneration. Cells 11(9): 1464.
32. Kawasaki H, Yamada T, Wada T, Kosugi S (2020) Current status and legal/ethical problems in the research use of the tissues of aborted human fetuses in Japan. Congenit Anom (Kyoto) 60(6): 166-174.

33. Ishii T, Eto K (2014) Fetal stem cell transplantation: Past, present, and future. World J Stem Cells 6(4): 404-420.

34. Park KI, Goo K, Jung K, Kim M, Kim I, et al. (2013) Therapeutic application of neural stem cells for neonatal hypoxic-ischemic brain injury. Neonatal Med 20: 343.

35. Willis CM, Nicaise AM, Peruzzotti-Jametti L, Pluchino S (2020) The neural stem cell secretome and its role in brain repair. Brain Res 1729: 146615.

36. Karvelas N, Bennett S, Politis G, Kouris NI, Kole C, et al. (2022) Advances in stem cell therapy in Alzheimer's disease: A comprehensive clinical trial review. Stem Cell Investig 9: 2.

37. Zakrzewski W, Dobrzyński M, Szymonowicz M, Rybak Z (2019) Stem cells: Past, present, and future. Stem Cell Res Ther 10(1): 68.

38. Henriques D, Moreira R, Schwamborn J, Pereira de AL, Mendonça LS, et al. (2019) Successes and hurdles in stem cells application and production for brain transplantation. Front Neurosci 13: 1194.